IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Appellants	:	Rodney J. Ho et al.
Application No.	:	10/757,775
Filed	:	January 14, 2004
For	:	LIPID-DRUG FORMULATIONS AND METHODS FOR TARGETED DELIVERY OF LIPID-DRUG COMPLEXES TO LYMPHOID TISSUES
Examiner	:	Umamaheswari Ramachandran
Art Unit	:	1627
Docket No.	:	3342-4557PT
Date	:	May 10, 2010

APPEAL BRIEF

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P.O. Box 1450
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Sir:

This appeal is from the decision of the Examiner, in an Office Action mailed November 9, 2009, finally rejecting claims 1-3, 5-9, and 15-17.

REAL PARTY IN INTEREST

The real party in interest is the University of Washington, a public university of the State of Washington having an address of 4311 – 11th Avenue NE, Suite 500, Seattle, WA 98105-4608.

RELATED APPEALS AND INTERFERENCES

Appellants' representative has not identified, and does not know of, any other appeals or interferences which will directly affect or be directly affected by or have a bearing

on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-3, 5-9, and 15-17 are pending in this application. Claims 10-14 are withdrawn. Claims 4 and 18-45 are cancelled. Claims 1-3, 5-9, and 15-17 were finally rejected in the Office Action dated November 9, 2009. Appellants appeal the final rejection of claims 1-3, 5-9, and 15-17, which are copied in the attached CLAIMS APPENDIX, along with withdrawn claims 10-14. Because independent claim 1 is not made obvious by any combination of the cited references, withdrawn claims 10-14 are also non-obvious and should be allowed.

STATUS OF AMENDMENTS

No Amendment After Final is enclosed with this brief. The last Amendment was filed February 21, 2007.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1

Claim 1 is directed to a lipid-drug complex (page 7, line 24 – page 8, line 23) for subcutaneous administration comprising at least one lipid molecule and at least one drug molecule having low aqueous solubility within a neutral pH range (Figures 1A-B; page 12, lines 1-10), the at least one drug molecule substantially dissociating from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5 (page 15, lines 24-30).

Dependent Claim 6

Claim 6 is directed to the lipid-drug complex of Claim 1, wherein the liposome is a unilamellar liposome (page 10, line 16-25).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The rejection of claims 1-3, 5, 7-9, and 15-17 under 35 U.S.C. §103(a) as being unpatentable over Kirpotin, U.S. Patent No. 6,110,491 ("Kirpotin").

2. The rejection of claim 6 under 35 U.S.C. §103(a) as being unpatentable over Kirpotin in view of Thibodeau, Molecular Engineering, 1991, pp 275-293 ("Thibodeau") and Konigsberg et al., U.S. Patent No. 5,258,499 ("Konigsberg").

3. The rejection of claims 1-3, 5-9, 15-17 under 35 U.S.C. §103(a) as being unpatentable over Bergeron et al., U.S. Patent No. 5,773,027 ("Bergeron") in view of Kirpotin.

ARGUMENT

Claims 1-3, 5-9, and 15-17 are pending in the current application. In an office action dated November 9, 2009 ("Office Action"), the Examiner rejected claims 1-3, 5, 7-9, and 15-17 under 35 U.S.C. §103(a) as being unpatentable over Kirpotin, U.S. Patent No. 6,110,491 ("Kirpotin"), rejected claim 6 under 35 U.S.C. §103(a) as being unpatentable over Kirpotin in view of Thibodeau, Molecular Engineering, 1991, pp 275-293 ("Thibodeau") and Konigsberg et al., U.S. Patent No. 5,258,499 ("Konigsberg"), and rejected claims 1-3, 5-9, and 15-17 under 35 U.S.C. §103(a) as being unpatentable over Bergeron et al., U.S. Patent No. 5,773,027 ("Bergeron") in view of Kirpotin. Applicants respectfully traverses all of these rejections.

ISSUE 1

1. The rejection of claims 1-3, 5, 7-9, and 15-17 under 35 U.S.C. §103(a) as being unpatentable over Kirpotin, U.S. Patent No. 6,110,491 ("Kirpotin").

Claim 1 of the current application is provided below, for the reader's convenience:

> 1. A lipid-drug complex for subcutaneous administration comprising:
>
> at least one lipid molecule;, and
>
> at least one drug molecule having low aqueous solubility within a neutral pH range; and
>
> wherein the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5.

Claim 1 is directed to a complex aggregation of one or more different types of complex organic compounds, referred to as "lipids." There are probably millions or more possible different types of lipid aggregates, each with a different number and type of lipid components, each with a different structure and/or chemical composition, and each with

different physical and chemical properties and characteristics. Patent applications are written to be understood by those ordinarily skilled in the art, and those familiar with chemistry and biochemistry well understand that a precise chemical characterization of complex lipid aggregations, containing hundreds, thousands, millions, or more lipid molecules, is not possible. Instead, classes of lipid aggregates are identified by bulk characteristics, including diameter, types of lipid components, and other such bulk characteristics, or by a physical property or characteristics, such as the characteristic of the lipid-drug complex, claimed in claim 1, that "the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5."

As admitted by the Examiner on page 4 of the Office Action, Kirpotin does not teach that the drug encapsulated in Kirpotin's drug-encapsulating liposomes "substantially dissociates from the lipid-drug complex within a pH range of 5.0-5.5." In other words, Kirpotin does not teach the currently claimed invention. In order to nonetheless read claim 1 onto Kirpotin, the Examiner states, on page 4 of the Office Action: "The dissociation of the drug from the complex at the claimed pH range is the property of the lipid-drug complex," by "lipid-drug complex" referring to Kirpotin's drug-encapsulating liposomes. This is, of course, a conclusory statement for which the Examiner offers no support in any cited reference, including Kirpotin. Of course, an obviousness-type rejection based on such a conclusory statement falls far short of the "rational underpinning" requirements set out by the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc.*, and discussed in M.P.E.P. § 2141(III):

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396.

In view of the millions of different possible lipid aggregates with different chemical and physical properties, it is nothing short of absurd for the Examiner to assert that a particular

property is inherent in all or any particular lipid aggregates without some support, suggestion, or authority for the assertion.

Apparently recognizing that such conclusory statements, lacking support from any cited reference, far fall short of the "rational underpinning" requirements for obviousness-type rejections, the Examiner attempts to shift the burden of proof onto Appellants:

> Regarding the claimed dissociation properties, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

However, the Examiner cannot shift the burden to Appellants simply by making a conclusory assertion, as discussed in M.P.E.P. § 2112(IV):

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) ... Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

As discussed in M.P.E.P. § 2112.01:

> **I. PRODUCT AND APPARATUS CLAIMS — WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT**
>
> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best,*562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

M.P.E.P. § 2112 makes it very clear that the Examiner must show that Kirpotin's drug-encapsulating liposomes are identical or nearly identical to the currently claimed lipid-drug complex. The Examiner has not attempted to make such showing, providing a single sentence statement suggesting that, because Kirpotin's drug-encapsulating liposomes contain lipids, and encapsulate drugs, they are sufficiently "identical" to allow for a rejection based on inherency.

There are many statements in Kirpotin and in the current application from which one of ordinary skill in chemistry or biochemistry would necessarily conclude that the rigid-lipid-bilayer liposomes created by Kirpotin's method are very different from the lipid-drug complex claimed in claim 1. On page 18 of the current application, an exemplary method for preparing the currently claimed lipid-drug complex is provided. The drug to be incorporated into the lipid-drug complex is dissolved in ethanol and mixed together with lipids. The mixture is evaporated and re-suspended in sterile phosphate buffer solution and then subjected to probe sonification until the uniform particle size of 50 nm to 80 nm is reached. The sonification step is carried out for somewhat under 30 minutes. By contrast, as discussed in Kirpotin in columns 9 and 10, Kirpotin first prepares rigid lipid bilayer liposomes

containing the polymer sodium polyacrylate "to form liposomes having a higher-inside/lower-outside gradient of a charged, polyionic polymer." Then, as discussed towards the bottom of column 10, beginning on line 44, of Kirpotin, the drug to be encapsulated in the liposomes is encapsulated by a "loading by pH precipitation" method. In this method, the pH gradient established across the liposomes is used to precipitate the drug to be loaded into the liposomes within the liposome. In general, as stated by Kirpotin beginning on line 34 of column 8, the internal pH of the liposomes is preferably at or near the minimum-solubility pH of the precipitated compound, or at a lower pH of 4 to 5.5 or an upper pH of 8.5 to 10. Thus, as clearly stated by Kirpotin, an encapsulated drug such as indinavir, appreciably soluble only at very low pH, is precipitated and thus unavailable for release or dissociation from the liposomes at the very pH range of 5.0 to 5.5 that the currently claimed lipid-drug complex allows the drug to dissociate. In other words, Kirpotin explicitly teaches that the precipitated drug within Kirpotin's drug encapsulating liposomes cannot dissociate from the liposomes in the pH range of about pH 5.0 to about pH 5.5 at which the drug dissociates from the currently claimed lipid-drug complex. The currently claimed lipid-drug complex is prepared by a very different method than Kirpotin's drug-encapsulating liposomes. Kirpotin's drug-encapsulating liposomes include the charged, polyionic polymer sodium polyacrylate, while the currently claimed lipid-drug complex does not. No one with even undergraduate level training in chemistry of biochemistry would conclude, or even suggest, that lipid aggregates prepared by entirely different methods would necessarily be identical, equivalent, or even similar. The fact that, in Kirpotin's drug-encapsulating liposomes, the drug is meant to be precipitated in the very pH range that the drug dissociates from the currently claimed lipid-drug complex, by itself, indicates that there is no basis for the Examiner's inherency claim.

Those ordinarily skilled in the art would immediately recognize that lipid-drug complexes and drug-encapsulating liposomes are very complex aggregates of thousands, millions, or more complex organic molecules. A single type of lipid can, under differing conditions, form bilayer spheroids, micelles, unilamellar structures, and quite possibly many hundreds of thousands of distinct types of aggregates. It is currently beyond the capability of analytical methods to precisely characterize all of these different types of lipid aggregates. None of the cited references provide precise characterizations of their claimed drug-encapsulating liposomes. However, one difference between the currently claimed lipid-drug complex and Kirpotin's drug-encapsulating liposomes is the fact that the currently claimed lipid-drug complex releases the drug from the lipid-drug complex within the pH range of pH

5.0 to about pH 5.5. Kirpotin's drug-encapsulating liposomes are considered to be stable in these pH ranges, and, even in the presence of ionophores, do not release their contents (*see* Kirpotin's Abstract). The Examiner's statement that the "dissociation of the drug from the complex of the claimed pH range is the property of the lipid-drug complex" is true only for the currently claimed lipid-drug complex, and not for the drug-encapsulating liposomes disclosed by Kirpotin. Clearly, this rejection must fail. According to M.P.E.P. § 2112, when there is every indication in the cited reference and current application that the disclosed drug-encapsulating liposomes of the cited reference differ substantially from the currently claimed lipid-drug complex, the Examiner cannot simply shift the burden to Applicants to prove that Kirpotin's drug-encapsulating liposome does not release the drug in a pH range from about pH 5.0 to about pH 5.5. Because claim 1 is not made obvious by Kirpotin, no claim that depends from claim 1 is made obvious by Kirpotin.

ISSUE 2

2. The rejection of claim 6 under 35 U.S.C. §103(a) as being unpatentable over Kirpotin in view of Thibodeau, Molecular Engineering, 1991, pp 275-293 ("Thibodeau") and Konigsberg et al., U.S. Patent No. 5,258,499 ("Konigsberg").

The rejection of claim 6 depends primarily on Kirpotin. As discussed under Issue 1, Kirpotin does not teach, mention, or suggest that for which it is cited. The Examiner cites Thibodeau and Konigsberg for teaching monolamellar liposomes used for antigen delivery and for targeting solid tumors. Again, these are entirely different problem domains, and the methods used by Thibodeau and Konigsberg differ significantly than those used to prepare the lipid-drug complex of the current invention. As discussed above, with respect to Issue 1, liposomes and other lipid aggregations are very complex entities, containing millions of individual lipid molecules, and can take many different forms, each having different chemical and biochemical properties. One property that distinguishes the current lipid-drug complex from other lipid aggregations is that the currently claimed lipid-drug complex releases the drug within a pH range of about 5.0 to 5.5. As discussed above, Kirpotin explicitly teaches that a drug remains precipitated in that pH range within Kirpotin's drug-encapsulating liposomes. Moreover, Kirpotin's drug-encapsulating liposomes include a polyionic polymer and are prepared to have a significant pH gradient across the lipid membrane, while the currently claimed lipid-drug complex does not include a polyionic

polymer and is made by a very different method. Neither Thibodeau nor Konigsberg teaches, mentions, or even remotely suggests a lipid aggregate or liposome that releases a complex drug within the pH range of pH 5.0 to pH 5.5. Clearly, the Examiner's conclusory statement that release of drug in that pH range is somehow inherent to all lipid aggregates, regardless of how they are prepared, cannot serve as the basis for an obviousness-type rejection under the "rational underpinning" standards promulgated by the Supreme Court in the *KSR* decision, as discussed in M.P.E.P. §2143(III).

ISSUE 3

3. The rejection of claims 1-3, 5-9, 15-17 under 35 U.S.C. §103(a) as being unpatentable over Bergeron et al., U.S. Patent No. 5,773,027 ("Bergeron") in view of Kirpotin.

The rejection of claims 1-3, 5-9, and 15-17 under 35 U.S.C. §103(a) as being unpatentable over Bergeron in view of Kirpotin clearly fails for the same reason that the rejection of these claims as being unpatentable over Kirpotin fails. Kirpotin does not teach, mention, or even remotely suggest the currently claimed lipid-drug complex that releases the drug in a pH range of about pH 5.0 to about pH 5.5. Bergeron also fails to teach, mention, or even remotely suggest drug dissociation from Bergeron's drug-encapsulating liposomes in that pH range, as admitted by the Examiner on page 7 of the Office Action. Again, in the rejection of the current claims as being unpatentable over Bergeron and Kirpotin, the Examiner makes the absurdly conclusory assumption that the "dissociation of the drug from the complex of the claimed pH range is the property of the lipid-drug complex," referring to Kirpotin's drug-encapsulating liposomes. However, as discussed above with regard to Issue 1, Kirpotin explicitly teaches otherwise. In Kirpotin's drug-encapsulating liposomes, the drug is meant to be precipitated within the drug-encapsulating liposome at a pH of about pH 5.0 to about pH 5.5. Just because a molecular aggregate contains a certain type of biomolecule, such as a lipid, does not mean that the aggregate is similar to another aggregate that contains the same biomolecule. As those with even undergraduate-level experience in chemistry and biochemistry well appreciate, there are hundreds or thousands of different types of aggregates that can be prepared by different methods, the aggregates having different properties, sizes, and structures. As one example, Bergeron's drug-encapsulating liposomes are reported by Bergeron as having diameters of between 100 nm and 300 nm, in contrast to the 50 nm to 80 nm diameters of the currently claimed lipid-drug complex, and are prepared by methods that

differ substantially from the methods employed to create the lipid-drug complex of the present invention. There is simply no basis to conclude that the drug-encapsulating liposomes of either Kirpotin or Bergeron have the property of releasing the drug within the pH range of about 5.0 to about 5.5. The Examiner cannot simply shift the burden to Applicants by citing references that do not teach, mention, or even remotely suggest lipid-drug complexes with the claimed drug-releasing property and that disclose drug-encapsulating liposomes prepared by different methods than those used to prepare the currently claimed lipid-drug complex. Because claim 1 is not made obvious by a combination of Bergeron and Kirpotin, no claim that depends from claim 1 is made obvious by Bergeron and Kirpotin.

CONCLUSION

All of the rejections of the current claims are based on an inherency assertion. However, the Examiner has failed to provide any evidence, reference, or citation that would in any way support this assertion. The currently-claimed lipid-drug complex is made by a different method than the methods by which Kirpotin's and Bergeron's drug-encapsulating liposomes are made, and has different physical characteristics than those reported for their respective drug-encapsulating liposomes by Bergeron and Kirpotin. Neither Kirpotin nor Bergeron teaches, discloses, or even remotely suggests that their drug-encapsulating liposomes release the encapsulated drug in a pH range of 5.0-5.5. There is no basis for the assertion that release of drug in this pH range is inherent in all drug-complexing lipid aggregates, or any particular type or class of drug-complexing lipid aggregate, other than the lipid-drug complex of the present invention.

Appellants respectfully submit that all statutory requirements are met and that the present application is allowable over all the references of record. Therefore, Appellants respectfully request that the present application be passed to issue.

Respectfully submitted,
Rodney J. Ho et al.
OLYMPIC PATENT WORKS PLLC

By _____
Robert W. Bergstrom
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CLAIMS APPENDIX

1. A lipid-drug complex for subcutaneous administration comprising:

at least one lipid molecule;, and

at least one drug molecule having low aqueous solubility within a neutral pH range; and

wherein the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5.

2. The lipid-drug complex of Claim 1, wherein the neutral pH range includes a range near pH 5.0 to about pH 8.

3. The lipid-drug complex of Claim 1, wherein the lipid and drug molecules are associated as a complex at a molar ratio of lipid-to-drug that is within a range of about 3:1 to about 100:1.

4. Cancelled.

5. The lipid-drug complex of Claim 1, wherein the lipid-drug complex is a liposome.

6. The lipid-drug complex of Claim 1, wherein the liposome is a unilamellar liposome.

7. The lipid-drug complex of Claim 1, wherein the drug is an anti-viral drug.

8. The lipid-drug complex of Claim 1, wherein the drug is an anti-HIV drug.

9. The lipid-drug complex of Claim 1, wherein the drug is indinavir, saquinavir, nelfinavir, or tenofovir disoproxil fumarate.

10. The lipid-drug complex of Claim 1, wherein the drug is an anti-fungal drug.

11. The lipid-drug complex of Claim 1, wherein the drug is an anti-bacterial drug.

12. The lipid-drug complex of Claim 1, wherein the drug is an immunomodulatory drug.

13. The lipid-drug complex of Claim 1, wherein the drug is an anticancer drug.

14. The lipid-drug complex of Claim 1, wherein the drug inhibits the growth of breast cancer.

15. The lipid-drug complex of Claim 1, wherein the lipid includes one or more of phospholipids, sphingolipids, cardiolipins, spingomyelin, glycolipids, gangliosides, cerebrosides, cholesterol, fatty acids, PEG derivatized lipids, monoglycerides, diglycerides, triglycerides.

16. The lipid-drug complex of Claim 1, wherein the lipid-drug complex is about 30 to about 150 nanometers in diameter.

17. The lipid-drug complex of Claim 1, wherein the lipid-drug complex is about 50 to about 80 nanometers in diameter.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.